



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: K. Edwards

U.S. Serial No.: 10/034,981

Filed: December 27, 2001

For: *Intravenous Valproate for Acute Treatment of
Migraine Headache*

Attorney Docket No.: NRI-001CN

Group Art Unit: 1615

Examiner: Fubara, B.

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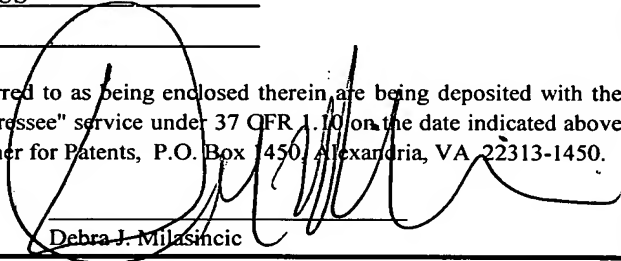
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Debra J. Milasincic

APPEAL BRIEF

As indicated in the notice filed on November 19, 2003 and received by the U.S. Patent Office on November 19, 2003, Appellant hereby appeals the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. For the reasons set forth in this brief, Appellant respectfully requests the Board of Patent Appeals and Interferences to reverse the Examiner's final rejection of the claimed subject matter.

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I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is K. Edwards.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellant, Appellant's legal representative or the assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-14 are pending in this application.

Claims 1-14 are on appeal and are set forth in Appendix A.

IV. STATUS OF THE AMENDMENTS

A notice of appeal was filed November 19, 2003.

V. SUMMARY OF THE INVENTION

Appellant's invention pertains to a method for the abortive treatment of acute migraine headaches by administering a bolus intravenous injection of valproate sodium, also referred to according to its tradename as Depacon™. The invention is based on the discovery that intravenous valproate is an alternative therapy for abortive treatment of moderate to severe prolonged acute migraine headache having equal or greater effectiveness than the traditional treatment using dihydroergotamine (DHE).

Appellant's invention pertains to a method for the abortive treatment of acute migraine headache in a subject comprising administering to the subject an effective dose of intravenous valproate such that abortive treatment occurs, e.g., acute migraine headache is lessened or reduced, in said subject.

Subjects having acute migraine headache are effectively treated without adverse side effects and the treatment can be administered to subjects having recently been treated with other migraine therapeutics, namely ergotamine or triptan, without significant drug-drug interactions.

VI. STATEMENT OF ISSUE PRESENTED FOR REVIEW

Appellant presents the following issue for review:

I. Whether claims 1-14 are unpatentable under 35 U.S.C. §103(a) as being obvious over Welch ("Drug Therapy: Drug Therapy of Migraine" The New England Journal of Medicine) in view of Walser (U.S. Patent No.5,432,176).

VII. GROUPING OF CLAIMS

Claims 1-14 are on appeal. Claim 1 is the only independent claim on appeal. Claim 1 is drawn to a method for the abortive treatment of acute migraine headache in a subject comprising administering to the subject having a migraine headache an effective dose of intravenous valproate such that the abortive treatment of acute migraine headache occurs.

Claims 2-14 directly depend from claim 1. Claim 2 is drawn to the method of claim 1, wherein administration is such that severity of acute migraine headache is lessened or reduced.

Claim 3 is drawn to the method of claim 1, wherein administration is such that duration of acute migraine headache is lessened or reduced.

Claim 4 is drawn to the method of claim 1, wherein administration is such that a symptom selected from the group consisting of nausea, photophobia, and phonophobia is lessened or reduced.

Claim 5 is drawn to the method of claim 1, wherein about 100mg to 2000mg of valproate is administered to a subject.

Claim 6 is drawn to the method of claim 1, wherein about 200mg to 1500mg of valproate is administered.

Claim 7 is drawn to the method of claim 1, wherein about 300mg to 1000mg of valproate is administered.

Claim 8 is drawn to the method of claim 1, wherein about 250mg to 750mg of valproate is administered.

Claim 9 is drawn to the method of claim 1, wherein about 500mg valproate is administered to the subject.

Claim 10 is drawn to the method of claim 1, wherein the valproate is administered to the subject over 30 minutes to 1 hour.

Claim 11 is drawn to the method of claim 1, wherein the valproate is administered to the subject over 15 to 30 minutes.

Claim 12 is drawn to the method of claim 1, wherein the valproate is administered to the subject over 5 to 15 minutes.

Claim 13 is drawn to the method of claim 1, wherein the valproate is administered to the subject over 1 to 5 minutes.

Claim 14 is drawn to the method of claim 1, wherein the valproate is administered to the subject in more than one dose.

VIII. ARGUMENTS

The present invention is directed towards a method for the abortive treatment of acute migraine headache in a subject comprising administering to the subject an effective dose of intravenous valproate such that abortive treatment in said subject occurs.

A. Claims 1-14 are patentable over the prior art of record.

Claims 1-14 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Welch ("Drug Therapy; Drug Therapy of Migraine". The New England Journal of Medicine) (Appendix B) in view of Walser (U.S. Patent No. 5,432,176) (Appendix C).

It is the Examiner's position that "the combined references teach treating migraines with valproate." The Examiner relies on Welch for teaching "the administration of 800mg valproate daily for migraine headache therapy." The Examiner points out that the amount administered in Welch (800mg) lies within the range of the claims at issue (100mg to 2000mg). The Examiner relies on Walser for teaching that "valproate can be administered by intravenous injection in 800 mg dosage."

The Examiner states that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to intravenously administer 800 mg of valproate to treat migraine because Walser intravenously administers 800 mg of valproate." The Examiner finds motivation to combine these references because "one having ordinary skill in the art would have been motivated to intravenously administer valproate since medications intravenously administered gets to the blood stream quicker."

For the reasons set forth below it is Appellant's position that the Examiner has failed to establish a *prima facie* case of obviousness. First, Appellant respectfully submits that the Examiner has misconstrued what the references teach, and as such the

prior art references, alone or combined, do not teach or suggest all the claim limitations. Appellant also submits that, at the time the invention was made, there was no motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references to arrive at the use of an intravenous administration of valproate for the abortive treatment of acute migraine headache. Appellant further submits that one of ordinary skill in the art would not have had a reasonable expectation of success in attempting to combine the prior art references to arrive at the claimed invention, at the time the invention was made.

1. The Examiner has misconstrued what the Welch reference teaches, and the reference, alone or combined with the Walser reference, fails to teach or suggest all of the claim limitations.

Appellant respectfully submits that the Examiner has misconstrued what the Welch reference teaches, and the reference, alone or in combination with the Walser reference, fails to teach or suggest all of the claim limitations. To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (C.C.P.A. 1974).

The Examiner takes the position that the Welch reference teaches “treating migraines with valproate.” This is an improper construction of what Welch teaches. In generalizing what Welch teaches, the Examiner has failed to appreciate the distinction between the prophylactic treatment of migraine headaches, *i.e.*, preventative treatment of migraine headaches, and the acute treatment of migraine headaches, *i.e.*, treatment of an already existing migraine headache.

Welch reviews drug therapies for migraines. Welch clearly separates his review of these therapies into two distinct topics, those that are for the “Symptomatic Treatment of Acute Migraine” (Table 1) and those that are for the “Prevention of Migraine” (Table 2). Valproic acid is indicated as a drug for the prevention of migraine (Table 2 and page 1481). Welch reviews Sorensen (1988) which first describes a benefit of valproate sodium (600 mg twice daily) for preventative therapy of migraine in a small open study of patients. Welch also reviews Hering and Kuritzky (1992) which describes a small clinical trial in which valproate sodium (800 mg daily oral dosage) was only moderately effective in preventing migraine.

Nowhere does Welch teach treating a subject having an acute migraine with valproate. The Examiner appears to consider all treatment of migraine, whether prophylactic or acute, as one indistinguishable concept to find suggestion for treatment of acute migraine in the Welch reference. This is in contrast to what the skilled artisan would understand, as evidenced by the Welch review itself, namely that prevention of migraine is a distinct indication from treatment of acute migraine. Proper characterization of the Welch reference results in only a teaching of daily oral valproate administration for the prevention of migraine.

Nothing in the Welch reference (or even in the Sorensen or Hering and Kuritzky references reviewed therein) even remotely teaches or suggests treatment of a subject having a migraine headache with an effective dosage of intravenous valproate such that the abortive treatment of acute migraine headache occurs.

Further, appellant submits that even within the class of drugs which includes sodium divalproax (oral valproic acid) and sodium valproate (intravenous valproic acid), the two drugs cannot be used interchangeably. The 800-1000 mg daily oral dosage of valproic acid listed in Table 2 is given as a twice-daily dose orally for prevention of migraine. This drug, by attaining circulating steady-state levels following daily usage for a week or more, can prevent migraine headache. In fact, since Dr. Welch published the 1993 NEJM article, sodium divalproax (oral valproic acid) has been FDA approved for the use of migraine prophylaxis.

By contrast, sodium divalproax (oral valproic acid) has not been approved for intravenous use. Nor has sodium valproax (oral valproic acid) been approved for acute migraine treatment. Only sodium valproate is used intravenously, and this is a different compound from sodium divalproax (oral valproic acid). Likewise, sodium valproate has not been demonstrated by a multi-centered, double blind study to be effective for migraine prophylaxis, and is not, at this time, approved for use for migraine prophylaxis. Thus, there is nothing in the teaching of Welch that would have suggested to the skilled artisan to substitute the daily oral valproic acid (sodium divalproax), of Welch with a bolus intravenous treatment of sodium valproate (intravenous valproic acid) to arrive at the instant invention.

Walser teaches intravenous administration of valproate for use in treatment of patients with chronic renal failure. Walser teaches that valproate can be administered in 800 mg dosage. Walser fails to teach anything regarding the treatment of subjects having migraine headache. Walser fails to rectify the deficiency in the teachings of

Welch. Thus, alone or combined these references fail to teach or suggest all of the claim limitations.

2. The Examiner has failed to show a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of Welch and Walser.

Appellant submits that in view of the teachings in the cited art, and the knowledge of the art generally, one of ordinary skill in the art would not have been motivated to combine the teachings of the cited art to produce the claimed invention. *Prima facie* obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Appellant contends that there is nothing in either of the two cited prior art references, or in the knowledge of the art generally, that would suggest to one of skill in the art that they should administer intravenous valproic acid for the abortive treatment of acute migraine headache.

The Examiner states that “one having ordinary skill in the art would have been motivated to intravenously administer valproate since medications intravenously administered gets to the blood stream quicker.” Appellant respectfully submits that based on the teachings of the prior art, and the knowledge of the art generally, the Examiner’s reasoning is erroneous. Nothing in Welch or Walser provides a suggestion or motivation to combine the teachings of these references in order to arrive at the claimed invention. Likewise, one of ordinary skill in the art, a physician, would not have been motivated to combine the teachings of the references to arrive at the claimed invention, based on the knowledge generally available in the art at the time of the invention. In light of the distinctions known between prophylactic migraine treatments, and acute migraine treatments as well as the distinction between intravenous valproic acid and oral valproic acid, the fact that “medications intravenously administered gets to the blood stream quicker” would not lead a person of ordinary skill in the art to combine the references to arrive at the claimed invention,

Appellant submits that in the Welch reference there are two distinct topics being reviewed, the “Symptomatic Treatment of Acute Migraine” and the “Prevention

of Migraine”. In Table 1, entitled “Drug Treatment of Migraine Attacks”, there is a list of medications that are used to treat and stop a migraine headache after the headache has begun, *i.e.*, acute treatments. Table 2 entitled “Prevention of Migraine” lists medications that are used at a constant or ‘steady state’ level to prevent occurrence of a migraine. Valproic acid is listed in Table 2 as a drug that can be used to prevent migraine. Neither valproic acid, nor any of the other therapies listed in Table 2 (prophylactic therapies) are listed in Table 1 for use to treat acute migraine attack (excepting the general analgesics).

Welch clearly teaches that the use of the medications listed in Table 1 to treat acute migraines is very different than the use of those listed in Table 2 to prevent migraines. Just as prevention of a disease is quite a different challenge from acute treatment once the disease has become manifest, so too, is the difference between acute treatment for migraine and prevention of a migraine. Thus the teachings of Welch fail to provide the motivation to use a drug listed as a prophylactic therapy to treat an acute migraine attack.

Appellant submits that Walser teaches the use of sodium valproate (intravenous valproic acid) for treating chronic renal failure, but nowhere teaches or suggests the use of intravenous valproic acid for other indications. Thus there is no motivation or suggestion in Walser to use intravenous valproic acid for any condition other than chronic renal failure. One of ordinary skill in the art would hardly have been motivated to combine the teachings of Welch and Walser in order to arrive at the current invention.

The court requires the examiner to show a motivation to combine the references that create the case of obviousness, in order to prevent the use of hindsight based on the invention to defeat patentability of the invention. See In Re Rouffet, 149 F.3d 1350, 1357. In Rouffet, the patent application was directed towards technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites, by changing the shape of the beam transmitted by the satellite’s antenna to a fan-shaped beam. Rouffet, 149 F.3d at 1353. The Board upheld the examiner’s obviousness rejection of the application in light of three prior art references. The Court of appeals however reversed finding that:

The board didn’t err in finding that the combination [of the prior art] contains all of the elements claimed in Rouffet’s application. However the

Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, the board did not identify any motivation to choose these references for combination. Id at 1357.

Similar to Rouffet, appellant contends that the Examiner erred in finding that one of skill in the art would find motivation to combine the Welch and Walser references in a manner that renders the claimed invention obvious. Walser only discusses using intravenous valproate to treat chronic renal failure. Welch only lists oral valproate as a migraine prophylactic. The Examiner has not pointed to any thing in either reference that would suggest to a person of ordinary skill in the art that these references could be combined to create the claimed invention. Nor is there a specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of the invention to make the combination. See Rouffet, 149 F.3d at 1357.

Further support for the position that there is nothing in the cited references, either alone or in combination, or in the knowledge generally available to one of ordinary skill in the art, that suggests the claimed invention can be found in In Re Fine. See In Re Fine, 837 F.2d 1071, at 1074 (Fed. Cir. 1988). In Fine, the invention claimed a system for detecting and measuring minute quantities of nitrogen compounds. Id at 1072. The examiner rejected the claims at issue based on two prior art references: U.S. Patent No. 3,650,696 (the Eads patent), which disclosed a method for separating, identifying, and quantitatively monitoring sulfur compounds; and U.S. Patent No. 3,746,513 (the Warnick patent), which was directed to a means for detecting the quantity of pollutants in the atmosphere. Fine, 837 F.2d at 1072, 1073. The examiner found that “substitution of the [nitric oxide] detector of Warnick for the sulfur detector of Eads would be an obvious consideration if interested in nitrogen compounds, and would yield the claimed invention.” Id at 1073.

On appeal, the court held that the PTO had failed to establish a *prima facie* case of obviousness because it failed to show some objective teaching in the prior art or the knowledge generally available to one of ordinary skill in the art, that would lead an individual to combine the relevant teachings of the references. See Fine, 837

F.2d at 1074. The court found that there was no support for or explanation of the examiners conclusion that “substitution of one type of detector for another in the system of Eads would have been within the skill of the art.” Id. The court further held that there was no suggestion in the Eads patent, which was focused on the unique difficulties inherent in the measurement of sulfur, to use that arrangement to detect nitrogen compounds. Id.

Much like the lack of suggestion to combine or modify the prior art references to arrive at the claimed invention in the Fine case, there is no suggestion in the Welch reference to use valproic acid for treatment of acute migraine attacks. Nor is there anything in Walser that would suggest using intravenous valproate to treat migraine. The Examiner’s reliance on the fact that “medications intravenously administered gets to the blood stream quicker” to provide motivation to intravenously administer valproate is inappropriate. Welch clearly teaches that there is a distinction between prophylactic migraine treatments and acute migraine treatments. One of ordinary skill in the art would also recognize the difference that exists between intravenous valproic acid and oral valproic acid. Thus the fact that intravenously administered medications get into the blood stream quicker, would not motivate one of ordinary skill in the art to combine the teachings of Welch and Walser to arrive at the instant invention.

Support for appellant’s position that there is no motivation to combine or modify the references to produce the claimed invention is also found in In Re Vaeck. In Re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). In Vaeck, the invention was directed towards “a chimeric (*i.e.*, hybrid) gene comprising (1) a gene derived from a ~~bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with~~ (2) a DNA promoter effective for expressing the *Bacillus* gene in a host cyanobacterium so as to produce the desired insecticidal protein.” Id. at 490. Of the eleven prior art references applied in various combinations against the claims, the primary reference (Dzelzkalns) taught the expression of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT) in cyanobacteria. Id. at 490,491. The secondary references collectively disclosed expression of genes encoding certain *Bacillus* insecticidal proteins in various bacterial hosts. Id. at 491. The examiner claimed that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by the secondary references for the CAT gene in the vectors described by the

primary reference in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. Id at 492.

On appeal the court held that the PTO had failed to establish a *prima facie* case of obviousness of the claimed subject matter. Vaeck, 947 F.2d at 493. The court found that the prior art did not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein. Id. The court held that “the expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.” Id. Furthermore, while the prior art disclosed “expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed cyanobacterial hosts....[w]hile it is true that bacteria and cyanobacteria are now both classified as prokaryotes, that fact alone is not sufficient to motive the art worker as the PTO contends.” Id at 493, 494.

Similar to Vaeck, there is no “suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art” in the instant case. See Vaeck, 947 F.2d at 495. Welch does not suggest using any of the prophylactic treatments for migraines to treat acute migraine attacks, nor does Walser suggest using valproic acid for anything other than treatment of chronic renal failure. Thus because the suggestion to combine the prior art references, cannot be found in the references themselves, or the knowledge generally available to one of ordinary skill in the art appellant contends that the Examiner erred by finding the claims at issue to be obvious.

Appellant finds further support for the position that the Examiner has failed to show a motivation or suggestion to combine the cited prior art references to arrive at the claimed invention in In Re Dembiczak. In Re Dembiczak, 175 F.3d 944 (Fed. Cir. 1999). In Dembiczak, the invention at issue was a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with leaves or trash, to resemble a Halloween-style pumpkin, or jack-o’-lantern. Id at 996. The patent application was rejected as being obvious in light of conventional trash bags in view of two other references which taught the construction of decorated paper bags in order to make them resemble a jack-o’-lantern. Dembiczak, 175 F.3d at 997. On appeal, the Federal Circuit overturned the Board’s finding of obviousness, holding that the Board failed to “particularly identify any suggestion, teaching, or motivation

to combine the children's art references with the conventional trash ... bag references." Id at 1000.

Much like the Board's findings in Dembiczak, appellant submits that the Examiner has not demonstrated how the Welch and Walser references, or the knowledge generally available to one of ordinary skill in the art, teach or suggest the combination of the reference teachings to arrive at the present invention. Id. By simply stating that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to intravenously administer 800 mg of valproate to treat migraine because Walser intravenously administers 800 mg of valproate", the Examiner has not identified any suggestion, teaching or motivation to combine the references to teach administration of intravenous valproate for the treatment of acute migraine. Appellant submits that the Examiner is simply taking "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability." Dembiczak, 175 F.3d at 999.

Unlike the decision in the Ryco v. AG- BAG case, appellant submits that the Examiner has not demonstrated a suggestion or motivation to combine references. Ryco Inc. v. AG-BAG Corp., 857 F.2d 1418 (Fed. Cir. 1988). In Ryco, the Court held that certain claims directed towards hydraulically operated brakes on an agricultural bagging machine were obvious in light of the prior art. Id at 1425. The claimed structure differed from the prior art machine only in the use of hydraulically operated rather than mechanically operated break means. Id. The court found that there was ample suggestion in the references for replacing the band brake of the prior art machine with the hydraulic brake of the claimed machine, based on the fact that the prior art references disclosed such brakes for performing the same function, albeit in a different environment. Id.

Unlike the Ryco case, the prior art in the instant case which discusses use of intravenous valproate (Walser reference) does not disclose the use of the drug for performing the same function (to treat migraines) as in the claimed invention. Instead, Walser only discusses use of intravenous valproate for treatment of chronic renal failure. Nor does Welch discuss using any form of valproate for the treatment of an acute migraine. Thus there is no suggestion in either of these references, or the knowledge generally available to one of ordinary skill in the art, to combine them in order to arrive at the claimed invention.

3. Based on the knowledge of one of ordinary skill in the art at the time of the invention, there would not have been a reasonable expectation of success in attempting to combine the prior art references to arrive at the claimed invention, at the time the invention was made.

The prior art can only be combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. See In Re Merck & Co., 800 F.2d 1091, (Fed. Cir. 186). The reasonable expectation of success must be assessed from the perspective of one of ordinary skill in the art, which in this case is a physician. See Life Technologies Inc. v. Clontech Laboratories Inc., 224 F.3d 1320 (Fed. Cir. 2000). The appellant respectfully submits that, at the time the invention was made, there was no reasonable expectation of success for using a well known prophylactic migraine treatment, which is administered orally, as a treatment for an acute migraine administered intravenously.

At the time of the invention, migraine prophylactic therapies and acute migraine therapeutics were not used interchangeably. This is due to different intracellular mechanisms which are considered to be required to be addressed in preventative (prophylactic) versus abortive (acute) treatments. Valproate has been used in the prior art only as a prophylactic treatment for migraines. Welch reviews oral valproate as a migraine prophylactic among a list of other art-recognized prophylactic therapies. Welch separately reviews acute migraine therapies. None of the prophylactic therapies of Welch are used as acute therapies (excepting the analgesics, and non-steroidal anti-inflammatory drugs used for general pain relief). Thus one of ordinary skill in the art would not have had a reasonable expectation of success in using a prophylactic migraine treatment to treat a patient suffering from acute migraine.

Likewise, one of ordinary skill in the art would not have had a reasonable expectation of success in deciding to use sodium valproate (intravenous valproic acid) instead of sodium divalproax (oral valproic acid) to treat a patient suffering from acute migraine. Since Dr. Welch published the 1993 N.E.J.M article, sodium divalproax (oral valproic acid) has been FDA approved for the use of migraine prophylaxis. By contrast, sodium divalproax (oral valproic acid) has not been approved for intravenous use. Nor has sodium divalproax (oral valproic acid) been

approved for acute migraine treatment. Only sodium valproate is used intravenously, and this is a different compound from sodium divalproax (oral valproic acid).

Likewise, sodium valproate has not been demonstrated by a multi-centered, double blind study to be effective for migraine prophylaxis, and is not, at this time, approved for use for migraine prophylaxis. Thus even within the class of drugs which includes sodium divalproax (oral valproic acid) and sodium valproate (intravenous valproic acid), the two drugs cannot be used interchangeably.

Nor does the Walser reference suggest to one of skill in the art a reasonable expectation of success in using intravenous valproic acid to treat acute migraine. Walser only discusses use of intravenous valproic acid to treat chronic renal failure. He does not suggest or even mention using the intravenous form of the drug as treatment for any other condition. Therefore, a physician would not have had a reasonable expectation of success when using intravenous valproic acid to treat migraine based on the teachings of Walser.

Appellant finds support for the position that there was no reasonable expectation of success in In Re Rinehart. In Re Rinehart, 531 F.2d 1048 (C.C.P.A. 1976). In Rinehart, the claims were directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure. Id at 1049. The claims were initially rejected as being obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence a solvent. Rinehart, 531 F.2d at 1050-1051. The court reversed finding that there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully. Rinehart, 531 F.2d at 1054.

Much like the Rinehart case, there is no reasonable expectation of success in combining the elements of the prior art to arrive at the instant invention. Id. The Welch reference does not suggest that valproate could be used to treat acute migraine headache. To the contrary, Welch teaches treatment of acute migraine separately from prophylactic treatment, and does not suggest that any medication used to treat migraines prophylactically could be used to treat acute migraines. Nor does Walser teach using intravenous valproic acid to treat acute migraine headache. Thus, a physician would not have a reasonable expectation of success in treating acute migraine using intravenous valproic acid based on the prior art. There is “nothing in

the record which would lead one of ordinary skill to anticipate successful” treatment of acute migraine with intravenous valproic acid. Rinehart, 531 F.2d at 1054.

Appellant submits that the instant case is much different than In re Merck & Co. In Re Merck & Co. Inc., 800F.2d 1091 (Fed. Cir. 1986). In Merck, the claims were directed to a method of treating depression with amitriptyline. Id at 1092. The Federal Circuit upheld an obviousness rejection of these claims based on a prior art disclosure that amitriptyline was a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess anti-depressive properties. Id. The Court read this prior art disclosure in view of other prior art that suggested that the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement (bioisosterism is the theory that the substitution of one atom or group of atoms for another atom or group of atoms having similar size, shape and electron density provides molecules having the same type of biological activity). Merck 800 F.2d at 1096. The Court combined these two prior art references with a research paper that compared the pharmacological properties of imipramine, and amitriptyline, and suggested clinical testing of amitriptyline as an antidepressant, to find that there was a reasonable expectation of success for one of ordinary skill in the art. Id at 1097.

Unlike the prior art in Merck, Welch does suggest the use of a prophylactic therapy for treatment of an acute migraine. Merck 800 F.2d at 1096-1097. Nor is there anything in the prior art generally that points to the therapeutic properties of valproate for the treatment of acute migraine. Oral valproic acid is FDA approved only for prophylactic migraine treatment, not acute migraine treatment. Nor can oral valproic acid (sodium divalproax) and intravenous valproic acid (sodium valproate) be used interchangeably. A physician possessed of the knowledge of the art generally would not have had a reasonable expectation of success when deciding to substitute the daily oral valproic acid (sodium divalproax) of Welch with a bolus intravenous treatment of intravenous valproic acid (sodium valproate) to arrive at the instant invention.

Overall, there is nothing in the prior art that would lead a person of ordinary skill in the art to believe there was a reasonable expectation of success in combining the prior art to arrive at the instant invention. The art generally teaches that there is a distinction between prophylactic treatments of migraine headache, and acute migraine therapies. One of ordinary skill in the art would also recognize the distinction between

oral valproic acid (sodium divalproax) and intravenous valproic acid (sodium valproate). As such, one of ordinary skill in the art would not have had a reasonable expectation of success in treating a patient with an acute migraine headache by administering intravenous valproic acid (sodium valproate).

IX. CONCLUSION

In view of all of the above, Appellants submit that claims 1-14 are patentable over the art made of record.

For at least the foregoing reasons, the Board should reverse the final rejection of claims 1-14.

Date: June 21, 2004

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